
PHARMACEUTICAL SCIENCES

**SUBMISSION OF AN "INVESTIGATIONAL NEW DRUG
APPLICATION" TO THE OFFICE OF GENERIC DRUGS (OGD)**

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PURPOSE

- To describe Office of Generic Drugs (OGD's) policy and procedures regarding submission of an Investigational New Drug Application (IND) for a bioequivalence study under the "Abbreviated New Drug Regulations; Final Rule," 57 FR 17,950 (April 28, 1992) (Title I Regulations). These IND's are called Bio-IND's to distinguish them from clinical IND's submitted to the new drug reviewing divisions of the Center for Drug Evaluation and Research. OGD will only accept IND's for bioequivalence studies (i.e., Bio-IND's).
 - The primary purpose of a Bio-IND is to ensure that the proposed product is safe for use in human test subjects and does not expose them to undue risk and untoward effects from the drug product.
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BACKGROUND

- FDA's regulations describe when an IND must be submitted for an *in vivo* bioavailability or bioequivalence study in humans (21 CFR § 320.31) and the required content of the IND (21 CFR § 312). The requirements for when an IND must be submitted were revised when the FDA published its Title I regulations to make the requirements consistent with current practice as it has evolved over the years.
 - Under the revised regulations (21 CFR § 320.31(a)), an IND is required to conduct an *in vivo* bioavailability or bioequivalence study in humans if:
 1. The test product contains a new chemical entity, or
 2. The study involves a radioactively labeled drug product, or
 3. The study involves a cytotoxic drug product.
 - An IND is required to conduct a bioavailability or bioequivalence study in
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humans using a drug product that contains an already approved "non-new" chemical entity if:

1. The maximum single or total daily dose in a single dose study in normal subjects or patients exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application (NDA) or an abbreviated new drug application (ANDA).
 2. The single or total daily dose in a multiple-dose study in normal subjects or patients exceeds that specified in the labeling of the drug product that is the subject of an approved NDA or ANDA.
 3. If a multiple-dose study is to be conducted on a controlled release drug product on which no single dose study has been completed.
 4. A bioequivalence study involves a clinical end point.¹
- A Bio-IND may be submitted to OGD for a bioequivalence study of any of the types described above **except** a study in which the test product contains a new chemical entity (21 CFR § 320.31(a)(1)).
 - In the past, OGD accepted Bio-IND's containing only a protocol for a proposed bioavailability or bioequivalence study, although Bio-IND's that contained all of the information required by 21 CFR § 312 were sometimes submitted. OGD's new policy is that in addition to a protocol, sufficient information must be submitted in a Bio-IND to enable an OGD bioequivalence reviewer and a review chemist to determine the safety of the formulation to be used in the proposed bioequivalence study. This Guide describes specifically what is required for a Bio-IND for a bioequivalence study conducted to support an ANDA.
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POLICY AND PROCEDURE

- **Contents of a Bio-IND**
 1. Protocol for conducting an *in vivo* bioequivalence study in humans; only one protocol per Bio-IND submission;
 2. Components and composition of the generic drug to be used in the bioequivalence study including the amounts of the active ingredient(s) and excipients;
 3. Tests and specifications for identity, strength, quality, and purity for active ingredient(s) and Certificates of Analysis of excipients;
 4. Method and place of manufacturing including the type of equipment,
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batch size (meeting the parameters described in CDER MAPP 5223.3 and 5223.1), and batch records;

5. Tests and specifications for the finished dosage form (Certificates of Analysis);
 6. Stability testing data on the drug product stored for three months at 40°C and 75% relative humidity including information on the container/closure system(s) used in the stability tests unless other conditions are appropriate for that product.
- OGD will refuse to accept a Bio-IND which does not contain the information described above.
 - Complete information on chemistry, manufacturing, and controls also must be included in the ANDA, even if such information, in whole or in part, was contained in the Bio-IND.
 - **Filing and Review Procedures**
 1. Filing of Bio-IND's - A Bio-IND received in the Document Room will be identified by its cover letter and standard form 1571. It will be given a number in the 15-000 series and entered into the MIS IND system.
 2. The Bio-IND will then be routed to the central CSO staff which will review the submission for acceptability and send out an acknowledgment letter under the signature of the Director, OGD. If the Bio-IND does not contain the information described in **POLICY AND PROCEDURE, Contents of a Bio-IND**, 1-6, a refuse to file letter will be issued and a firm will have to correct the deficiencies and resubmit the Bio-IND.
 3. If a Bio-IND is determined to be acceptable for filing, the thirty-day safety review clock will start on the date of receipt of the submission.
 4. The central CSO staff will send one copy to the appropriate OGD Chemistry Branch based upon the pharmacological class of the drug to be studied, another copy to the Division of Bioequivalence or the appropriate NDE reviewing Division, and a third copy to the Document Room to be filed.
 - a. Normally, the Division of Bioequivalence will review the protocol for the bioequivalence study to ensure that the safety of subjects entering the study will not be compromised. If a protocol raises a medical issue such as proposing to administer a dose not addressed in the labeling, a medical officer in NDE will be consulted.

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- b. Information on chemistry, manufacturing, and controls will be reviewed by one of the two Divisions of Chemistry to ensure the safety of the study volunteers. A more detailed review will be conducted of the chemistry, manufacturing and controls information that is later submitted in the ANDA.
- 5. A CSO will be assigned the responsibility to track the Bio-IND through the review process, including checking periodically with the reviewing divisions on the status of the reviews. If the CSO determines that the safety reviews will not be completed within thirty days, he or she will inform the firm and may request that the start of the study be deferred until the reviews are completed. Upon completion of the safety reviews, OGD will notify the firm that the study may begin or that the study has been placed under a clinical hold pursuant to 21 CFR § 312.42.
 - 6. The chemistry and bioequivalence reviews of the Bio-IND, when completed, will be sent back to the central CSO staff. That staff will prepare the appropriate action letter for the signature of the Director, OGD.
 - 7. A bioequivalence study completed under a Bio-IND should be submitted in the ANDA which it supports. No bioequivalence studies should be submitted as amendments to Bio-IND's.
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EFFECTIVE DATE

This guide is effective upon date of publication.

NOTE

¹Paragraphs 1-3 are contained in 21 CFR § 320.31(b). Paragraph 4 reflects current practice.